REMARKS

Reconsideration and allowance are respectfully requested.

Claims 22, 25-32, 35-36 and 40-43 are pending. Claims 25 and 40 were withdrawn from consideration by the Examiner; their rejoinder is requested.

The negative limitation --said process being performed without ethyleneglycol bis(2-aminoethylether) tetraacetic acid-- is intended to distinguish over processes that are performed in its presence. Other features of claim 27 are found, inter alia, at page 6, line 19, to page 8, line 3, and page 10, line 28, to page 11, line 21, of the specification. Note that --a lower critical solution temperature-- is supported implicitly by "a lower critical temperature for dissolution" at page 11, lines 3-4, of the specification. It is known to a skilled artisan that both phrases have the same meaning, although the former may be more popular in the art than the latter.

Information Disclosure Statement

To satisfy their continuing duties of candor and good faith, Applicants bring to the Examiner's attention the related subject matter in U.S. patent applications, Serial Nos. 10/333,468, 10/333,473, 10/544,541, 10/544,542, 10/546,275, 10/567,728, 11/587,427, 11/885,222, and 11/885,246. He is invited to consider their prosecution histories and the evidence of record in those applications, which are accessible through the IFW, in view of the Federal Circuit's holding in *McKesson Information Solutions v. Bridge Medical*, 82 USPQ2d 1865 (Fed. Cir. 2007). To avoid duplication of those materials in the PTO's records, reference to the IFW is encouraged but Applicants would be ready to submit copies of these materials for the Examiner's review if he prefers.

35 U.S.C. 112 – Written Description

The specification must convey with reasonable clarity to a person of skill in the art that applicant was in possession of the claimed invention as of the filing date sought. See *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). This description includes "words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." *Lockwood v. American Airlines*, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). An invention disclosed in the specification that inherently performs a function or has a property, operates according to a theory, or has an advantage necessarily discloses that function, theory, or advantage even though the specification says nothing explicit about the characteristic. See *In re Smythe*, 178 USPQ 279, 285 (C.C.P.A. 1973). Thus, an amendment introducing an inherent characteristic of the invention into the claims is not prohibited by the written description requirement. See *id*. A specification need not teach, and preferably omits, what is well known in the art. See *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986).

Claims 22, 26-36 and 41-43 were rejected under Section 112, first paragraph, because they allegedly contain new matter not supported by the specification as originally filed. Applicants traverse because the challenged limitations would be recognized as implicitly described in the original disclosure by a person of skill in the art.

It was alleged that "nude rat" in claims 22 and 27 is new matter. The Examiner contends that paragraph [0024] does not explicitly or implicitly support nude rats as claimed. Applicants notes that paragraph [0024] reads as follows:

> Animals can be used as recipients for transplantation in the present invention **include, but are not limited to**, nude mouse, rat, mouse, guinea pig, and rabbit

(emphasis added).

It was well known in the art that a mouse and a rat belong to the class of rodents, and that they are closely related to each other. Thus, the skilled artisan reading paragraph [0024] would easily understand that a nude rat can be used as a recipient for transplantation in the claimed invention. In other words, paragraph [0024] implicitly teaches that a nude rat as well as a nude mouse can be used as a recipient for transplantation.

For the foregoing reasons, Applicants submit that recitation of a nude rat in claims 22 and 27 does not add new matter to the original disclosure.

In view of the Examiner's statement at the bottom of page 4 of the Office Action, the phrase "homo- **or** co-polymer" (emphasis added) is recited in claims 22 and 27. Thus, the objection is moot.

Similarly, Applicants submit that deletion of "a strong hydration force" in claim 27 moots the objection on page 5 of the Office Action.

Withdrawal of the written description rejection is requested.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 22, 26-36 and 41-43 were rejected under Section 112, first paragraph, because the specification allegedly "does not reasonably provide enablement for **any** polymer that changes its hydration force as broadly claimed" (emphasis added). Applicants traverse because the teachings in

this specification enable the skilled artisan to practice their invention as presently claimed.

Here, the present amendments require use of a "homo- or co-polymer of N-isopropylacrylamide" in Applicants' claimed invention. On pages 5-6 of the Office Action, the Examiner did find that making a non-human animal having transplanted cancer cells with "a cell culture supported coated with poly N-isopropylacrylamide" was enabled. Applicants submit that the present claims are consistent with this finding of enablement, especially in view of paragraph [0021] of the specification.

It was also alleged that performing the method in a nude rat is not enabled. Applicants disagree. The Examiner admits on page 8 of the Office Action that human cancer cells are maintained in an animal model if the animal is immunocomprised. Here, a nude rat is an immunocompromised animal. Therefore, use of a "nude rat" would not require undue experimentation to practice the claimed invention.

Withdrawal of the enablement rejection is requested.

35 U.S.C. 112 – Definiteness

Claims 22, 26-36 and 41-43 were rejected under Section 112, second paragraph, as allegedly being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

It was alleged that the terms "weak" and "strong" as they describe the hydration force is indefinite. Claim 27 is amended to delete these terms and to recite "lower critical solution temperature" as defined in the specification.

Claim 29 is rewritten as suggested by the Examiner on page 10 of the Office Action.

The term "transplantable" in claim 31 is deleted. Claim 33 is canceled.

The term "living" in claim 35 is deleted.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 27-31, 33, 35 and 42-43 were rejected under Section 102(b) as allegedly being anticipated by Koezuka et al. (Nippon Nogei Kagaku Kaishi, 68:783-792, 1994). Applicants traverse.

Koezuka discloses a method for culturing human cancer cells by using a thermoresponsive polymer (PNIPAAm) as well as a substrate conjugated collagen and this polymer. Koezuka's substrate (i.e., a mixture of collagen and PNIPAAm) corresponds to the cell culture support of Applicants' claimed invention. In other words, Koezuka's substrate is a PNIPAAm-collagen substrate, which is different from the cell culture support used in Applicants' claimed process. According to Koezuka, the PNIPAAm-collagen substrate is changed from a solid phase to a liquid phase by changing the temperature, and this change detaches cultured cells for recovery. Moreover, Koezuka suggested that the human cancer cell lines are cultured in a gel. In contrast, Applicants' cell culture support as used in the presently claimed process never changes to a liquid phase. This is evident from the entirety of their specification.

Further, in accordance with Koezuka's method, ethyleneglycol bis(2-aminoethylether) tetraacetic acid (EGTA) is indispensable for detachment of cultured cancer cells from the substrate without using a proteolytic enzyme

such as trypsin. But EGTA is not required to practice Applicants' claimed invention.

Applicants submit that these features of their claimed invention are sufficient to distinguish over the cited document so any other incorrect allegations about its disclosure are not disputed here, but the opportunity to dispute them in the future is reserved.

Koezuka does not anticipate the claimed invention because the cited document fails to disclose all limitations of independent claim 27. Moreover, claims 28-31, 35 and 43 depending from claim 27 are also not anticipated by the cited document because all limitations of an independent claim are incorporated in claims depending therefrom. See *In re McCarn*, 101 USPQ 411, 413 (C.C.P.A. 1954). Note that claim 42 depends from claim 22, not claim 27.

Withdrawal of the Section 102 rejection is requested because the cited document fails to disclose all limitations of the claimed invention.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a one of ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR Int'l v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of

hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry should be made as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. But a claim that is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 22, 27-31, 33, 35 and 42-43 were rejected under Section 103(a) as allegedly being unpatentable over over Koezuka et al. (Nippon Nogei Kagaku Kaishi, 68:783-792, 1994) in view of Sakai (JP 05-192138). Applicants traverse.

Koezuka discloses a mixture of PNIPAAm and collagen for use as a substrate (i.e., a PNIPAAm-collagen substrate) to cultivate human cancer cells. Although the PNIPAAm-collagen substrate corresponds to the cell culture support of Applicants' invention, Koezuka's substrate is not used in the manner required by their claims. In other words, the substrate of the primary document is a PNIPAAm-collagen substrate, which is different from the cell culture support used in Applicants' process. According to Koezuka, the PNIPAAm-collagen substrate is changed from a solid phase to a liquid phase by changing the temperature, and this change detaches the cultivated cells from the cell culture support. Koezuka's cell culture support does not satisfy the requirements of Applicants' presently claimed invention. Further, Koezuka suggests that the human cancer cell lines are cultured in a gel. In contrast, Applicants' cell culture support as used in their claimed process

never changes to a liquid phase. Thus, Koezuka's use of a PNIPAAm-collagen substrate is not analogous to use of a cell culture support according to Applicants' claimed invention.

Sakai describes a method of cultivating skin cells comprising: preparing a cell culture support which has a surface of its base coated with a polymer having an upper or lower critical temperature for dissolution in water in a range of 0-80°C, cultivating skin cells on the cell culture support at a temperature not higher than the upper critical temperature for dissolution or at a temperature not lower than the lower critical temperature for dissolution, and thereafter adjusting the temperature to above the upper critical temperature for dissolution or below the lower critical temperature for dissolution, whereby the cultured skin cells are detached.

Sakai teaches, however, that this method is applied only to skin cells. It neither teaches nor makes obvious that the method can be applied to other normal types of cell or any kind of cancer cell. Moreover, Sakai does not make obvious that when detached cancer cells are in the form of a sheet, they are brought into contact with a carrier at the time the cultivation is completed and the cancer cells can then be detached intact from a cell culture support together with the carrier.

In this regard, the Examiner alleged **without providing evidence** that the claims of Sakai encompass skin cells that are cancer cells, that skin and cancer cells overlap (i.e., cancer cells can be skin cells), that skin cells and cancer cells share significant similarities in culture, and that skin cells and cancer cells can be cultured under similar conditions (page 17, lines 9-16 in the non-final Office Action). Applicants respectfully request that the Examiner provide evidence to support these allegations.

While Sakai's invention provides cultured skin cells for transplantation and treatment of burns, Applicants' present invention provides a human cancer-cell transplanted nude mouse or nude rat that can be employed in a

method of selecting an anti-tumor agent. Thus, the object of the presently claimed invention is entirely different from that of Sakai's invention. Therefore, one of ordinary skill in the art would never consider that Sakai's skin overlaps or includes a sheet of human cancer cells as required by Applicants' invention. Thus, Sakai is not analogous art and is cited here only by the use of hindsight.

Applicants submit that the cited documents teach away from their claimed invention and show a lack of a reasonable expectation of success to make their claims. Thus, the claimed invention is patentable over Koezuka in view of Sakai. As taught in paragraph [0004] of the specification, the transplanted cancer cells obtained by prior art techniques have poor take and the size and weight of the transplanted sheet of cancer cells varies so greatly from one animal to another that evaluation of various anti-cancer agents to reveal any significant differences in their efficacy is difficult.

Further, in accordance with Koezuka's method, ethyleneglycol bis(2-aminoethylether) tetraacetic acid (EGTA) is indispensable for detaching cultured cancer cells from the substrate without using a proteolytic enzyme such as trypsin. But EGTA is not required to practice Applicants' claimed invention.

The object of the present invention is to provide a novel non-human animal model free from the problems of the prior art (see paragraph [0004] of the specification). The present invention is characterized in that cancer cells can be transplanted efficiently by using a sheet of cancer cells. Such efficient transplantation of cancer cells into a non-human animal could not been achieved using prior art techniques (see paragraph [0007] of the specification).

With regard to common general knowledge in the art as of March 4, 2004 (i.e., the filing date of the priority application) and whether there was

a reasonable expectation of success, only the following cancer cell-transplanted animals were known (see paragraph [0003] of the specification):

1) knockout mice deprived of anti-oncogenes such as APC and p53, and

2) animals in which cancer has been developed by various methods such as the use of chemicals and other carcinogenic agents and direct transplantation of human cancer cells of interest.

But use of these animals raised the following problems (see paragraphs [0003] and [0004] of the specification). Among these animals, anti-oncogene knockout mice require fairly sophisticated (and expensive) genetic manipulation. Cancer development with carcinogenic agents requires a prolonged time to accomplish. Transplanting cancer cells has the advantage of giving experimental results in a short period of time. On the other hand, in the prior art, the transplanted cancer cells have poor take and the size and weight of the transplanted cancer tissue vary so greatly from one animal to another that evaluation of various anti-cancer agents involves difficulty in revealing any significant differences in their efficacy. Reasons for this defect include the poor take of the transplanted cancer cells and the leakage of the cancer cells suspension from the site of transplantation. Therefore, Applicants believed it was desirable to improve functions of the cells to be transplanted.

The present invention was made to solve the foregoing drawbacks. As taught in paragraph [0015] of the specification, Applicants' present invention is characterized by the following features.

If human cancer cells are cultivated on a cell culture support coated on a surface with a polymer (the hydration force changes in a range of 0-80°C), the cultivated cells can be detached from the support without a proteolytic enzyme (e.g., trypsin) being used. Only a simple change in the cultivation temperature is required. As a result, the detached cell sheet is free from damage it would have received if treated with a proteolytic enzyme such as

trypsin. Since detachment of the cultivated human cancer cells involves no enzyme treatment, the adherent protein remains intact and assures good take after transplantation. If the human cancer cells are in a sheet form, there is another advantage in that the leakage of a cell suspension from the site of transplantation is effectively suppressed to allow for efficient preparation of a human cancer cell-transplanted animal.

As illustrated in Examples 1 and 2 of Applicants' specification, their invention has made it possible to form cancer tissue in a cancer cell-transplanted animal in a manner superior to the prior art. None of the documents cited thus far taught or made obvious such an advantageous technique that efficiently produces a human cancer cell-transplanted animal by directing attention to the properties of the cells recovered without proteolytic enzyme treatment.

The present invention has made it possible to obtain a non-human animal model in which size and/or shape of cancer tissue in the animal can be controlled by preparing a sheet of the cancer cells in a specified size and/or shape. Therefore, Koezuka in view of Sakai would not have made the claimed process obvious with a reasonable expectation of success at the time Applicants' invention was made.

The presently claimed invention is patentable over Koezuka in view of Sakai because their combined disclosures do not suggest or otherwise make obvious independent claim 22 or 27. In other words, claims 28-31, 35 and 42-43 are not obvious from the cited documents because the characteristics of an independent claim are incorporated in its dependent claims. M.P.E.P. § 2143.03 citing *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

Withdrawal of the Section 103 rejection is requested because the claims would not have been obvious to one of ordinary skill in the art with a reasonable expectation of success when this invention was made.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /Gary R. Tanigawa/
Gary R. Tanigawa
Reg. No. 43,180

901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100